Increased Basic Fibroblast Growth Factor Levels in Serum and Blister Fluid from Patients with Vitiligo

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Basic fibroblast growth factor (bFGF) is a pleiotropic growth factor which has a high capacity for stimulating normal melanocyte proliferation and suppressing melanogenesis. The close and complicated relationship between bFGF, melanocyte proliferation and melanogenesis raises the theoretical possibility that bFGF may also be involved in the pathomechanism leading to vitiligo. The aim of this study was to compare the serum and suction blister fluid bFGF levels of vitiligo patients (9 females, 11 males) with those of healthy controls (3 females, 8 males). Vitiliginous skin-blower fluid bFGF levels and serum levels were significantly higher in vitiligo patients compared with healthy normal controls. Our data indicate that bFGF might be involved in the pathogenetic chain of events leading to vitiligo. Further studies are needed to define the exact role of bFGF and various other melanocytic mitogens in this disease. Key words: basic fibroblast growth factor; vitiligo.

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Paracrine linkage between keratinocytes and melanocytes within the epidermis plays an important role in cutaneous pigmentation and melanocyte growth, function and localization. Basic fibroblast growth factor (bFGF) is a pleiotropic growth factor that has mitogenic, morphogenic and angiogenic effects on various cell types of mesodermal and neurodermal origin. There are 4 isoforms of bFGF (18, 22, 23 and 24 kDa) which are all synthesized from the same mRNA via alternative translational start codons (1–4). Although bFGF has a high capacity to stimulate normal melanocyte proliferation, keratinocytes do not secrete it at concentrations sufficient to stimulate melanocyte stimulation, even during response to various stimuli, and thus several researchers believe that there is no link between epidermal pigmentation and the action of bFGF in the normal epidermis (5). bFGF in itself has no effect on melanocyte growth, but it stimulates proliferation of melanocytes in vitro when combined with growth hormone (GH) and/or insulin-like growth factor 1 (IGF-1) (6–8). Although α-melanocyte stimulating hormone (α-MSH) does not lead to the production of pigment in human skin melanocytes, it promotes DOPA oxidase activity and melanin density in medium with bFGF (7). bFGF in culture medium is mitogenic to pigmented cells, but suppresses the melanogenesis in a dose-dependent fashion (8). Moreover, bFGF plays a critical role in the transformation of normal human melanocytes to melanoma (9). Expression of bFGF mRNA and protein is detected in almost 100% of melanoma tumors in situ, as well as in most cell lines derived from metastatic melanomas. Inhibition of bFGF synthesis or function in melanoma cell lines leads to their growth suppression (10).

Vitiligo is a common skin disorder characterized by areas of depigmentation resulting from loss of melanocytes in the epidermis. Although there have been considerable advances in the elucidation of pathomechanisms leading to the disease, its precise etiology remains obscure.

The close and complicated relationship between bFGF, melanocyte proliferation and melanogenesis raises the theoretical possibility that bFGF may also be involved in the pathomechanism leading to vitiligo. The goal of the present investigation was to identify a possible linkage between bFGF and melanocyte destruction in patients with vitiligo by comparing their bFGF serum levels with those of healthy controls and the suction blister fluid of their lesional skin vs. that of normal skin and that of controls.

MATERIAL AND METHODS

Nine female and 11 male vitiligo patients (age 10–49 years) who attended the Dermatology Department of Cerrahpaşa Medical Faculty between May 1998 and July 1999 were enrolled in the study after giving their informed consent. The diagnosis of vitiligo was based mainly on clinical evaluation. The patients had had vitiligo for 1–22 years; all had widespread vitiligo and none of them were active during the procedures. Of 12 patients who had received treatment for vitiligo, 4 had been treated with PUVA, 1 had applied methoxalen solution (0.1%) following topical steroid therapy ≥1 year previously and 7 had applied topical steroids for ≥1 year. Three female and 8 male healthy volunteers (age 20–55 years) served as controls. The autologous suction blister was formed by a special device consisting of 3 pipes, 0.8 cm in diameter, connected to a negative pressure pump with a hose 1 m in length and 0.5 cm in diameter. This pump also served as a vacuum extractor device (max. –760 mmHg). For both patients and controls, room temperature was constant and blister formation time was 1–2 h. Autologous suction blisters, 0.8 cm in diameter, were formed on vitiliginous and normally pigmented skin and blister fluids were aspirated in order to measure bFGF levels.

Blister fluids from vitiliginous and normally pigmented skin of the
Table I. Mean (± SD) levels of bFGF (pg/ml) in skin-blister fluid and serum from vitiligo patients and healthy controls

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Skin</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitiligo patients</td>
<td>20</td>
<td>16.3 ± 12.8</td>
<td></td>
</tr>
<tr>
<td>Vitiligious skin</td>
<td>11</td>
<td>11.9 ± 11.1</td>
<td>11.8 ± 6.8</td>
</tr>
<tr>
<td>Normally pigmented skin</td>
<td>11</td>
<td>4.7 ± 0.4</td>
<td>7.0 ± 2.9</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>114</td>
<td>4.7 ± 0.4</td>
<td>7.0 ± 2.9</td>
</tr>
</tbody>
</table>

Patients and from the skin of the healthy controls, patient sera and control sera were stored at −70°C until assessment of bFGF levels using a bFGF ELISA kit (QIA14, Calbiochem) and an EL-500 Boehringer ELISA reader. Statistical analysis was performed by means of the Mann–Whitney U test.

RESULTS

Vitiligious skin-blister fluid bFGF levels and serum levels were significantly higher in patients with vitiligo compared to healthy normal controls (p < 0.001). No difference in bFGF levels was seen between blister fluid from pigmented and non-pigmented skin (Table I).

DISCUSSION

The increased levels of bFGF observed are in agreement with those reported from in vitro cultures of pluripotent zebrafish embryonal stem cells where bFGF stimulated proliferation of melanocytes, but suppressed melanogenesis (8). Interestingly, when the cultured wild-type cells were injected into albino blastula-stage embryos, melanocytes developed in host embryos only in the absence of bFGF. No melanocytes appeared when cultured cells with bFGF were injected.

In a study (11) of the effects of growth mitogens for human melanocytes, including bFGF, on the cytotoxicity of 4-tetrayl butylphenol (4-TBP) to melanocytes, it was found that deprivation of bFGF from melanocyte cultures resulted in reduced cytotoxicity to 4-TBP. Similar results were obtained with treatment of melanocytes with an inhibitor of the tyrosine kinase bFGF receptor. These results suggest that bFGF increases the susceptibility of melanocytes to the cytotoxic effects of 4-TBP and, therefore, that it might also be involved in “idiopathic” vitiligo.

In contrast, in a study on the role of melanocytic mitogens in repigmentation of vitiligo (12), 4 mitogens, including bFGF, stimulated melanocyte migration, thus indicating that this factor may have a role in vitiligo healing, in clear contradiction to our findings.

Although we have clear evidence that bFGF is involved in controlling melanocyte growth, proliferation, localization and function, there are as yet very few studies on the role of this factor in pigmentation disorders, particularly vitiligo. We believe that analyzing the role of various melanocytic mitogens in the development of vitiligo might lead to a better understanding of the pathomechanism of this disease.

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REFERENCES